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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,363	GABERT, JEAN	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2004 and 08 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-57,59,61 and 62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-57, 59, 61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This case has been transferred to examiner Teresa Strzelecka in Art Unit 1637 because examiner Spiegler left the USPTO.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 8, 2004 and February 8, 2005 has been entered.

3. Claims 43-62 were previously pending. Applicant amended claims 43, 52, 59, 61 and 62, and cancelled claims 58 and 60. Claims 43-57, 59, 61 and 62 are pending and will be examined.

4. Applicant's amendments and arguments overcame the following: objection to claims 43-62; rejection of claims 43-62 under 35 U.S.C. 112, second paragraph.

5. Applicant's arguments are addressed below in the "Response to Arguments" section.

6. In the firs paragraph of Remarks filed December 8, 2004, Applicant requested that the examiner have the Patent Office enter the Correspondence Address Indication Form filed March 11, 2003. Examiner checked the PALM records, and the correct address has been entered, which is further substantiated by the fact that Applicant receives Office communications mailed to this very address. Applicant is advised to contact the Electronic Business Center at 866-217-9197 to resolve the issue of electronic access.

Priority

7. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. No translation has been provided for this priority application,

therefore it is not clear if claims 43-57, 59, 61 and 62 are entitled to the priority of the filing date, which is October 30, 1997.

Therefore, claims 43-57, 59, 61 and 62 are given a priority date of October 29, 1998.

Response to Arguments

8. Applicant's arguments filed December 8, 2004 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 43-62 under 35 U.S.C. 112, first paragraph, written description, Applicant argues the following:

a) The specification describes at page 3, line 20, indiscriminate amplification of all types of fusion genes, and the specification describes, on page 3, lines 19-20, use of a single pair of primers for the anchored PCR.

However, the lines pointed to by Applicant do not provide such support, as can be seen from their content (specification, page 3, lines 19-24, as amended on July 10, 2001):

"The so-called semi-specific PCR technique employed is performed in such a way as to identify the junction fragment in the breakpoint region, and the sequence being then analysed. This article does not then teach asymmetric amplification to amplify the whole fusion genes and to reveal only genes implicated in the rearrangement."

Therefore, there is nothing in this paragraph that refers to "indiscriminate reverse transcription". Further, on page 7 of the specification, Applicant states the following with respect to RT-PCR (lines 25-28):

"Suitable sequences include a cassette with about 40 to 60 nucleotides with 10 to 20 T-patterns on one end or, alternatively, a random repeated nucleotide pattern."

Neither one of these primers would produce "indiscriminate" reverse transcription of RNA, since a primer with poly(dT) amplifies only RNA molecules with poly(dA) tails, not any RNA molecule, therefore it does not contribute to "indiscriminate" amplification, and a primer with repeated nucleotide pattern would not do it, either. Therefore, Applicant has no support for the term "indiscriminately reverse transcribing".

The situation is not improved by Applicant claim 48, which is drawn to "random" portion comprising a sequence of 10 to 20 (dT)s or a "sequence of random nucleotide pattern". Poly(dT) is not a random sequence. As to the "random nucleotide pattern", any sequence has a random nucleotide pattern, since Applicant did not define what this term means. Therefore, amplification with the primer of claim 48 will not be "indiscriminate".

b) Applicant further argues that RACE technology, which uses anchored primers, was described in the reference "PCR Primer: A laboratory Manual", which Applicant submitted in the response to a previous office action, is well known in the art and is described in steps (a)-(c) of claim 43. Applicant concludes: "The applicants have demonstrated, by reference to the above-noted textbook, that PCR using an "anchored" primer was known at the time of the present invention by those of ordinary skill in the art as "Classic RACE".

First, the facts. Applicant claims a method in which RNA is reverse transcribed using a primer with "random" sequence at the 3' end and a "unique" sequence at the 5' end. The next step involves amplification with one primer complementary to cDNA (second primer) and another primer complementary to the 5' end of the RT primer (third primer). Finally, in step c), the resulting amplification product is further amplified with two more primers, one complementary to the cDNA (fourth primer) and the other complementary to the 5' portion of the RT primer. Therefore, Applicant claims a method which involves five primers, one for reverse transcription and four for

cDNA amplification, with primers two and four related by the fact that primer four binds 3' to primer two on the cDNA sequence, and primers three and five bind to the 5' portion of the RT primer. The only disclosure of primers provided by Applicant is on page 21 and 22, where Applicant discloses reverse transcription with a primer of SEQ ID NO: 2 and subsequent amplification with primers of SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5. No relationship is provided between primers with SEQ ID NO: 3, 4 and 5 and SEQ ID NO: 2, or between primers with SEQ ID NO: 3-5. Further, there are only four primers, whereas Applicant claims five.

Second, the fact that a method is known in the art does not mean that it provides support for Applicant's claims, unless a reference to such method was specifically incorporated by reference in the specification. There is no mention of RACE anywhere in the specification, and RACE is only one example of anchored PCR methods. By Applicant standards anyone could claim methods and compounds which were previously disclosed without specific incorporation by reference of such methods or compounds into the specification. As stated by MPEP 2163.02:

> **2163.02 Standard for Determining Compliance With the Written Description Requirement**
>
> The courts have described the essential question to be addressed in description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied

upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under **35**

U.S.C.112, first paragraph - description requirement, or denial of the benefit of the filing date of a previously filed application, as appropriate.

Therefore, Applicant's disclosure provides no support for using a method with five primers which have a specific relationship with respect to each other, and, consequently, claims 43-57, 59, 61 and 62 lack written description.

c) Applicant proceeds to cite case law, which is misapplied, since the three cited cases refer to claims containing chemical compounds and written description issues concerning genus-species and genus-subgenus. Applicant quotes Nelson v. Bowler (1 USPQ2d 2076). The issue in this case was whether Nelson had support for written description and enablement of a subgenus of claimed compounds in the parent application. In the instant case the issue is whether Applicant provided any support for the claims, and the answer to this is clearly no.

Applicant move to argue that In re Filstrup and In re Herschler provide support for Applicant's assertion that the invention has proper written description. Applicant cites a paragraph from In re Filstrup which contains the following statement:

"...a sufficient basis is provided if "the specification is so worded that the necessary and only reasonable construction to be given the disclosure by one skilled in the art" is one which will lend clear support to the claim.", and a paragraph from In re Herschler, which contains the statement:

"It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations."

Applicant's disclosure does not even come close to conveying clearly support for the claimed subject matter, as detailed above. Therefore, Applicant cites case law, which not only is not applicable to the instant invention, but clearly points out deficiencies in Applicant's disclosure.

The rejection is maintained in a restated version.

B) The rejection of claims 58 and 60 under 35 U.S.C. 102(b) as anticipated by Morris was rendered moot by claim cancellation. Applicant argues that claim 61 was allowable over Morris et al., was rewritten as an independent claim. However, claim 61 was rejected under 35 U.S.C. 103(a) over Morris et al., Holtke et al. and Stratagene Catalog, therefore it was not allowable.

The rejection is maintained.

C) Applicant traverses the following rejections: rejection of claims 43-48 and 57 under 35 U.S.C. 103(a) over Nisson et al. and Holtke et al., rejection of claims 49-54 under 35 U.S.C. 103(a) over Nisson et al., Holtke et al. and Felix et al.; rejection of claims 55 and 56 under 35 U.S.C. 103(a) over Nisson et al., Holtke et al., Felix et al. and Kaneko et al. and rejection of claim 62 under 35 U.S.C. 103(a) over Nisson et al., Holtke et al., Felix et al. and Stratagene Catalog on the basis that Nisson et al. fail to teach detectably labeled cDNA products and does not suggest such products or incorporating a detectable label.

However, Nisson et al. do teach detection of cDNA with labeled probes (col. 6, lines 39-67; col. 7, lines 1-5) and also specifically teaches labeling cDNAs (col. 10, lines 36-37). Holtke et al. teach incorporation of labeled nucleotides into amplification products. Further, it is the combination of Nisson et al. and Holtke et al. that provides the necessary limitations to address all of the claims.

D) Regarding the rejection of claims 59 and 61 under 35 U.S.C. 103(a) over Morris et al., Holtke et al. and Stratagene Catalog, Applicant argues that Morris et al. teaches only two primers, neither one of which is anchored, and the probes of Morris et al. are labeled, whereas the claimed probes are not required to be labeled.

First, claim 61 as amended is drawn to two primers, the first of which is characterized as being complementary to a target gene, and the second primer, complementary to a first part of an anchored primer used to transcribe cDNA from mRNA. Therefore, Applicant does not claim an anchored primer, but a primer complementary to it. The limitation of a first primer being complementary to a target gene, without specifying the structure (i.e. sequence) of that target gene, does not distinguish the claimed primer from any other primer complementary to any other target gene. Further, the limitation of a second primer being complementary to a 5' portion of an anchored primer does not carry any weight, either, since a sequence of the anchored primer has not been provided. Therefore, Morris et al., by teaching two primers, teaches the kit. As to the argument that Morris et al. teach labeled probes, whereas claimed probes are not required to be labeled, Applicant argues a limitation which is not present in the claims.

The rejection is maintained as a 102(e), since Applicant did not define the term "DNA chip", and, therefore, a single probe bound to a solid support is considered to be a "DNA chip".

Claim Interpretation

9. Applicant did not define the term "anchored primer", therefore, any primer containing a 3' random portion and a 5' non-random sequence will be considered to be "anchored".

10. Applicant did not define the term "unique 5' portion", therefore any sequence is considred to be "unique".

11. Applicant did not define a term "random portion". However, according to claim 48, "random portion" consists of a sequence of 10 to 20 (dT)s or "a sequence of random nucleotide pattern".

12. Applicant did not define the term "a sequence of random nucleotide pattern". Since any sequence has, in principle, a random nucleotide pattern, any sequence anticipates this term.

13. Applicant did not define the term "DNA chip", therefore, a single probe bound to a solid support is considered to be a "DNA chip".

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 43-57, 59, 61 and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has not provided support for some of the limitations introduced into the claims as amended on February 17, 2004.

A) The limitation "indiscriminately reverse transcribing" is not supported by the specification. Applicant did not define the term. On page 7 of the specification, Applicant states the following with respect to RT-PCR (lines 25-28):

"Suitable sequences include a cassette with about 40 to 60 nucleotides with 10 to 20 T-patterns on one end or, alternatively, a random repeated nucleotide pattern."

Neither one of these primers would produce "indiscriminate" reverse transcription of RNA, since a primer with poly(dT) amplifies only RNA molecules with poly(dA) tails, not any RNA molecule, therefore it does not contribute to "indiscriminate" amplification, and a primer with repeated nucleotide pattern would not do it, either. Therefore, Applicant has no support for the term "indiscriminately reverse transcribing".

The situation is not improved by Applicant claim 48, which is drawn to "random" portion comprising a sequence of 10 to 20 (dT)s or a "sequence of random nucleotide pattern". Poly(dT) is not a random sequence. As to the "random nucleotide pattern", any sequence has a random nucleotide pattern, since Applicant did not define what this term means. Therefore, amplification with the primer of claim 48 will not be "indiscriminate".

B) The limitations of steps b) and c) of claim 43 are not supported by the specification. Step b) involves amplification with one primer complementary to cDNA (second primer) and another primer complementary to the 5' end of the RT primer (third primer). Finally, in step c), the resulting amplification product is further amplified with two more primers, one complementary to the cDNA (fourth primer) and the other complementary to the 5' portion of the RT primer. Therefore, Applicant claims a method which involves five primers, one for reverse transcription and four for cDNA amplification, with primers two and four related by the fact that primer four binds 3' to primer two on the cDNA sequence, and primers three and five bind to the 5' portion of the RT primer. The only disclosure of primers provided by Applicant is on page 21 and 22, where Applicant discloses reverse transcription with a primer of SEQ ID NO: 2 and subsequent amplification with primers of SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5. No relationship is provided between primers with SEQ ID NO: 3, 4 and 5 and SEQ ID NO: 2, or between primers with SEQ ID NO: 3-5. Further, there are only four primers, whereas Applicant claims five. No relationship is provided between the sequences of primers with SEQ ID NO: 3-5 and the sequences of target genes, i.e., what part of the target sequence is amplified by any of these primers.

C) The limitation of claims 45 and 51 of detectably labeled nucleotides bound indirectly to a marker selected from the group consisting of digoxigenine, biotin and fluorophore is not supported

by the specification. Lines 1-3 of page 6 of the specification disclose markers bound to deoxynucleotides, but do not disclose indirect binding or define it.

D) The limitation of claim 61 of a second primer complementary to a unique 5' portion of an anchored primer is not supported by the specification. The only disclosure of primers provided by Applicant is on page 21 and 22, where Applicant discloses reverse transcription with a primer of SEQ ID NO: 2 and subsequent amplification with primers of SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5. No relationship is provided between primers with SEQ ID NO: 3, 4 and 5 and SEQ ID NO: 2, or between primers with SEQ ID NO: 3-5. Therefore, Applicants did not provide a description of a primer which is complementary to a 5' unique portion of an anchored primer.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claim 61 is rejected under 35 U.S.C. 102(a) as being anticipated by Morris et al. (U.S. patent No. 5,770,421; cited in the previous office action).

Given the broadest reasonable interpretation of the claims, based on the "Claim Interpretation" section above, the claimed kit comprises:

1) A first primer being complementary to and binding specifically with cDNA of said target gene. This encompasses any primer having any degree of complementarity to and hybridizing to cDNA of any gene.

2) A second primer being complementary to and binding specifically with a first part of a "unique" 5' portion of an anchored primer. This encompasses any primer having any degree of complementarity to and which binds or hybridizes to any 5' portion of any sequence. Absent any definition in the specification with respect to what a "unique" 5' portion is or what is meant by an "anchored primer", the limitation has been broadly interpreted as comprising any 5' portion of any sequence.

It is also noted the recitation of "used to reverse transcribe said cDNA from mRNA transcribed from said fusion gene" is considered to be only a statement of purpose and intended result. This claim language does not result in any structural differences between the claimed invention and the product set forth by Morris et al.

3) At least one probe specific for cDNA encoded by said partner gene, said at least one probe being bound to a solid support. This encompasses a probe bound to a solid support. Applicant did not define the term "DNA chip", therefore any solid support with at least one probe is considered to be a DNA chip.

Morris et al. teach methods of detecting the NPM/ALK fusion gene, including PCR and nucleic acid hybridization (see cols. 2-3, for example). Morris et al. teach the use of two primers, a first primer being complementary to and binding specifically with cDNA of a target gene or fusion partner (NPM/ALK) and a second primer being complementary to and binding specifically with a first part of a "unique" 5' portion of an anchored primer (see col. 6, 21-23, for example). Morris et al. also teach probes specific for fusion genes (col. 6, lines 28-35; col. 17, lines 48-67; col. 18, lines

1-10; col. 19, lines 59-67; col. 20, lines 1-49, for example), which are immobilized on solid supports (= DNA chips) (col. 20, lines 42-49). Morris et al. teach the above reagents can be packaged in a kit (cols. 4, lines 9-12 and col. 12, lines 1-10).

18. Claim 61 is rejected under 35 U.S.C. 102(e) as being anticipated by Morris et al. (U.S. patent No. 5,770,421; cited in the previous office action).

Given the broadest reasonable interpretation of the claims, based on the "Claim Interpretation" section above, the claimed kit comprises:

1) A first primer being complementary to and binding specifically with cDNA of said target gene. This encompasses any primer having any degree of complementarity to and hybridizing to cDNA of any gene.

2) A second primer being complementary to and binding specifically with a first part of a "unique" 5' portion of an anchored primer. This encompasses any primer having any degree of complementarity to and which binds or hybridizes to any 5' portion of any sequence. Absent any definition in the specification with respect to what a "unique" 5' portion is or what is meant by an "anchored primer", the limitation has been broadly interpreted as comprising any 5' portion of any sequence.

It is also noted the recitation of "used to reverse transcribe said cDNA from mRNA transcribed from said fusion gene" is considered to be only a statement of purpose and intended result. This claim language does not result in any structural differences between the claimed invention and the product set forth by Morris et al.

3) At least one probe specific for cDNA encoded by said partner gene, said at least one

probe being bound to a solid support. This encompasses a probe bound to a solid support. Applicant did not defined the term "DNA chip", therefore any solid support with at least one probe is considered to be a DNA chip.

Morris et al. teach methods of detecting the NPM/ALK fusion gene, including PCR and nucleic acid hybridization (see cols. 2-3, for example). Morris et al. teach the use of two primers, a first primer being complementary to and binding specifically with cDNA of a target gene or fusion partner (NPM/ALK) and a second primer being complementary to and binding specifically with a first part of a "unique" 5' portion of an anchored primer (see col. 6, 21-23, for example). Morris et al. also teach probes specific for fusion genes (col. 6, lines 28-35; col. 17, lines 48-67; col. 18, lines 1-10; col. 19, lines 59-67; col. 20, lines 1-49, for example), which are immobilized on solid supports (= DNA chips) (col. 20, lines 42-49). Morris et al. teach the above reagents can be packaged in a kit (cols. 4, lines 9-12 and col. 12, lines 1-10).

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 43-48, 57, 59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (U.S. Patent No. 5,547,838; cited in the previous office action) and Holtke et al. (Cell. Mol. Biol., vol. 41, pp. 883-905, 1995; cited in the previous office action).

A) Regarding Claim 43, Nisson et al. teach an in vitro diagnostic method for detecting translocation of DNA sequences (t(8;21)) involved in cancer (acute myelogenous leukemia

(AML)), said translocation forming at least one rearranged fusion gene, said at least one rearranged fusion gene comprising a target gene and a partner gene, said method comprising the steps of:

a) indiscriminately reverse transcribing RNA extracted from a patient sample with a first primer, said first primer being a random anchored primer, said reverse transcribing producing patient cDNA, said anchored primer comprising a unique 5' portion and a 3' random portion (Nisson et al. teach reverse transcribing patient's RNA using a RACE procedure, where the primer contains a random portion poly (dT) and a 5' unique portion (= anchored primer) (col. 5, lines 25-41, col. 9, lines 20-26).);

b) amplifying all of the patient cDNA with a first pair of primers, said first pair of primers comprising a second primer and a third primer, said second primer being complementary to and binding specifically with cDNA of said target gene and said third primer being complementary to and binding specifically with a first part of the unique 5' portion of said anchored primer, said amplifying all of the patient cDNA producing a first collection of amplified products containing a first 5' target gene portion and a first 3' anchor portion (Nisson et al. teach amplifying cDNA with a pair of primers, one of which is specific (= complementary to and binding specifically) for the AML1 gene, and the other for the unique sequence at the 5' end of the anchored primer, producing a collection of amplified products (col. 5, lines 45-50, but see also col. 9, lines 26-33).);

c) amplifying said collection of amplified products with a second pair of primers in a nested amplification reaction, said second set of primers comprising a fourth primer and a fifth primer, said fourth being complementary to and binding specifically with said target gene at a position 3' to said second primer, said fifth primer containing a sequence which binds to at least a portion of said first pad of the unique 5' portion of said anchored primer, said amplifying said collection producing a second collection of amplified products containing a second 5' target gene portion and a second 3'

anchor portion, said second collection of amplified products further comprising detectably labeled nucleotides incorporated into said products during amplification (Nisson et al. teach amplifying the resulting product in a nested PCR reaction using a target-specific primer which binds 3' to the second primer and a unique sequence primer (col. 6, lines 18-23). Nisson et al. teach labeling cDNA molecules (col. 10, lines 36, 37).);

d) contacting said second collection of amplified products with at least one nucleic acid probe or at least one plurality of nucleic acid probes, wherein said at least one nucleic acid probe or each of said plurality of nucleic acid probes is specific for a partner gene, under conditions wherein any cDNA corresponding to said partner gene of the fusion gene present in said collection will hybridize with said probe (Nisson et al. teach contacting the amplified products with a probe specific for the partner gene (col. 6, lines 40-53; col. 7, lines 6-13 and 58-67).), and

e) detecting any detectably labeled cDNA from said second collection of amplified products bound to said probe as an indication of translocation of DNA sequences (Nisson et al. teach detection of the cDNA-probe complexes as an indication of the presence of the translocation (col. 7, lines 14-23).).

Regarding claim 44, Nisson et al. teach any one of the first primer, the second primer, the third primer, the fourth primer and the fifth primer is 25 to 40 nucleotides in length (col. 7, lines 60 and 62; col. 9, lines 22-64).

Regarding claim 48, Nisson et al. teach said first primer consists of a sequence containing a cassette of 40 to 60 nucleotides, wherein said 3' random portion comprises a sequence of 10 to 20 (dT)s (col. 9, lines 20-24 and 50-52).

Regarding claim 57, Nisson et al. teach identifying said partner gene of the fusion gene from binding of said probes (col. 6, lines 40-53; col. 7, lines 28-42 and 58-67).

Regarding claim 61, Nisson et al. teach kits comprising probes and primers for detection of target and partner fusion genes (col. 8, lines 59-65). Nisson et al. teach a primer complementary to cDNA of the target gene and a primer complementary to the unique 5' portion of the anchored primer (col. 5, lines 33-49; col. 9, lines 20-34). Nisson et al. teach probes specific for the cDNA of the partner gene (col. 6, lines 40-53; col. 7, lines 28-42 and 58-67).

B) Nisson et al. teach the detection of the translocation by using labeled probes, but do not teach that a label is incorporated into the amplification product, or probes bound to a solid support.

C) Regarding claim 43, Holtke et al. teach incorporating DIG-dUTP into a PCR product using the DIG (digoxygenine) system (page 884, column 1; pages 886-887, 889-890, 897 and 898). Holtke et al. teach the DlG-labeled PCR products can be detected on membranes, with the PCR ELISA plate, or can be analyzed by streptavidin-coated microtiter plates (page 888). More specifcally, Holtke et al. teach the use of the DIG labeling system can be used in RT-PCR assays (page 887).

Regarding claim 45, Holtke et al. teach DIG-labeled nucleotides (e.g., DIG-dUTP) (page 886, second paragraph).

Regarding claims 46, 47 and 59, Holtke et al. teach DIG-labeled PCR products can be detected by probes bound on an ELISA plate (page 888, first paragraph; Fig. 8). Since Holtke et al. teach at least one probe bound to a solid support (= ELISA plate), Holtke et al. teach a DNA chip. Further, Holtke et al. teach probes bound to a solid support via biotin-streptavidin interaction (page 899, first paragraph; Fig. 8).

Accordingly, in view of the teachings of Holtke, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nisson et al. to have included the steps of using the digoxygenine labeling and detection system,

and therefore, have incorporated a label into the PCR product for subsequent detection of a translocation. One of ordinary skill in the art would have been motivated to have used the DIG labeling and detection system of Holtke et al., because, as stated by Holtke et al., "this label does not occur naturally, high affinity antibodies were readily available from development of diagnostic and therapeutic reagents, the label is chemically, well accessible, it can be derivatized, and coupled to linkers and to nucleotides, its size and hydrophilicity enables the incorporation of hapten labeled nucleotides into nucleic acid probes by DNA and RNA polymerases" (see page 884). Furthermore, the skilled artisan would have been motivated to use the DIG labeling and detection system because Holtke et al. teach the DIG system "enables further applications due to the possibility to bind labeled nucleic acids specifically to solid phases, e.g., microtiterplates and magnetic beads", and concludes that the DIG system is one of "the most successful labeling and detection systems", since it is "proven to have advantages regarding both sensitivity and specificity" (pages 884 and 903).

21. Claims 49-54 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (U.S. Patent No. 5,547,838; cited in the previous office action) and Holtke et al. (Cell. Mol. Biol., vol. 41, pp. 883-905, 1995; cited in the previous office action), as applied to claims 43 and 61 above, and in further view of Felix et al. (U.S. Patent No. 6,368,791; cited in the previous office action).

A) The teachings of Nisson et al. and Holtke et al. are presented above. Specifically, Nisson et al. and Holtke et al. teach an in vitro diagnostic method for detecting translocation of DNA sequences (t(8;21)) involved in cancer (acute myelogenous leukemia (AML)), said translocation forming at least one rearranged fusion gene, said at least one rearranged fusion gene comprising a target gene and a partner gene, wherein the method comprises a RACE-based PCR screening assay. While Nisson et al. and Holtke et al. teach improved methods for diagnosing the presence or onset

of AML by analyzing the t(8;21) translocation, they do not teach the method wherein the target gene is MLL.

Regarding claim 49, Nisson et al. teach AML, acute myeloid leukemia (Abstract; col. 1, lines 10-27).

Regarding claim 51, Holtke et al. teach DIG-labeled nucleotides (e.g., DIG-dUTP) (page 886, second paragraph).

Regarding claim 52, Holtke et al. teach DIG-labeled PCR products can be detected by probes bound on an ELISA plate (= solid surface) (page 888, first paragraph; Fig. 8). Since Holtke et al. teach at least one probe bound to a solid support (= ELISA plate), Holtke et al. teach a DNA chip.

Regarding Claim 53, Holtke et al. teach the method of claim 52 wherein said marker is digoxygenine, said detecting comprises contacting said marker with anti-digoxygenine antibodies coupled to an enzyme (alkaline phosphatase, β-galactosidase or horseradish peroxidase), said enzyme being capable of reacting with a substrate of said enzyme to release a detectable product (page 884, second paragraph; page 890, first paragraph).

B) Regarding claims 49 and 62, Felix et al. teach translocations in the MLL gene at chromosome band 11q23 are associated with most cases of ALL which occur during infancy and with most monoblastic variants of AML which occur during the first four years of life (col. 1, lines 29-51, col. 15, lines 5-25). That is, rearrangements of MLL are known to be associated with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) is children. Felix et al. teach that PCR can be used for identifying MLL gene rearrangements (see col. 3, lines 34-60; col. 7, lines 30-46; Fig. 1 and 2; Examples 1-7).

Regarding claim 50, Felix et al. teach probes specific for MLL fusion partner genes (col. 31, lines 13-29).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nisson et al. and Holtke et al. so as to have detected remangements in the MLL gene of Felix et al. The motivation to do so, provided by Felix et al., would have been that detecting MLL translocations allowed designing appropriate treatment for leukemias caused by MLL translocations in children (col. 1, lines 35-45; col. 3, lines 54-61).

22. Claims 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (U.S. Patent No. 5,547,838; cited in the previous office action), Holtke et al. (Cell. Mol. Biol., vol. 41, pp. 883-905, 1995; cited in the previous office action), and Felix et al. (U.S. Patent No. 6,368,791; cited in the previous office action), as applied to claims 43-54 above, and further in view of Delattre et al. (New England J. Med., vol. 331, pp. 294-299, 1994).

A) The teachings of Nisson et al., Holtke et al. and Felix et al. are presented. Specifically, the references teach an in vitro diagnostic method for detecting translocation of DNA sequences involved in cancer (e.g., leukemia), said translocation forming at least one rearranged fusion gene, said at least one rearranged fusion gene comprising a target gene and a partner gene, wherein the method comprises a RACE-based PCR screening assay. The references do not teach the cancer is a solid tumor, such as Ewing tumor.

B) Regarding claims 55 and 56, Delattre et al. teach Ewing sarcoma (solid tumor), which is associated with a t(11;22) translocation or a (21,22) gene rearrangement, generating fusion proteins of the EWS gene with FLI1 gene or ERG gene (Abstract; first and third paragraphs of page 2 of the HTML version). Delattre et al. teach detection of fusion transcripts using reverse transcription of

RNA obtained from solid tumors and PCR using gene-specific primers (page 3 of the HTML version, last paragraph; page 4 of the HTML version).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have detected the translocations of Ewing's sarcoma of Delattre et al. by the method of gene translocation detection in cancer of Nisson et al., Holtke et al. and Felix et al. The motivation to do so, provided by Delattre et al., would have been that, as stated in the first paragraph:

"Ewing's sarcoma, the second most common malignant bone tumor of children and young adults, is an aggressive osteolytic tumor with a marked propensity for dissemination. Accurate and rapid diagnosis is essential for clinical management, but classification of the neoplasm can be difficult because the microscopical appearance of the tumor is not specific."

23. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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April 29, 2005

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